IN THIS ISSUE

Highlighted research articles .......................... 920

NEWS IN BRIEF

Important news stories affecting the community ........ 924

NEWS IN DEPTH

Why First-Line Nivolumab Is No Better than Chemo ...... 927
Taking the Guesswork Out of Stopping TKIs .............. 928

RESEARCH WATCH

Selected highlights of recent articles of exceptional significance from the cancer literature .......... 929

ONLINE

For more News and Research Watch, visit Cancer Discovery online at http://cancerdiscovery.aacrjournals.org/content/early/by/section.

VIEWS

In The Spotlight

Fast-TRKKing Drug Development for Rare Molecular Targets .... 934
A.R. Parikh and R.B. Corcoran
See article, p. 963

Reversion Mutations with Clinical Use of PARP Inhibitors: Many Genes, Many Versions .......... 937
S.M. Domchek
See article, p. 984
See article, p. 999
See article, p. 1006

Spotlight on Ibrutinib in PCNSL: Adding Another Feather to Its Cap ............... 940
A. Lakshmanan and J.C. Byrd
See article, p. 1018

REVIEW

New Horizons for Precision Medicine in Biliary Tract Cancers ...... 943
J.W. Valle, A. Lamarca, L. Goyal, J. Barriuso, and A.X. Zhu

RESEARCH BRIEFS

A Next-Generation TRK Kinase Inhibitor Overcomes Acquired Resistance to Prior TRK Kinase Inhibition in Patients with TRK Fusion–Positive Solid Tumors .. 963
Précis: Parallel development of the first-generation TRK TKI ronaltrectinib with the next-generation TKI LOXO-195 allowed for rapid use of LOXO-195 to treat patients with acquired larotrectinib resistance.
See commentary, p. 934

Exome Sequencing of African-American Prostate Cancer Reveals Loss-of-Function ERF Mutations ........ 973
Précis: Sequencing of an African-American prostate cancer cohort identified ERF as a tumor suppressor in prostate cancer and shows that increasing ethnic diversity enhances the discovery of potential cancer drivers.
Secondary Somatic Mutations
Restoring RAD51C and RAD51D
Associated with Acquired Resistance
to the PARP Inhibitorrucaparib in
High-Grade Ovarian Carcinoma........... 984
O. Kondrashova, M. Nguyen, K. Shield-Armit,
A.V. Tinker, N.N.H. Teng, M.I. Harrell, M.J. Kuiper,
G.-Y. Ho, H. Barker, M. Jasim, R. Prakash, E.M. Kass,
M.R. Sullivan, G.J. Brunette, K.A. Bernstein,
R.L. Coleman, A. Floquet, M. Friedlander,
G. Kichenadasse, D.M. O’Malley, A. Oza,
J. Sun, L. Robillard, L. Maloney, D. Bowtell on
behalf of the ADCS Study Group, H. Giordano,
M.J. Wakefield, S.H. Kaufmann, A.D. Simmons,
T.C. Harding, M. Raponi, I.A. McNeish, E.M. Swisher,
K.K. Lin, and C.L. Scott
Précis: In patients with high-grade ovarian
carcinoma treated with the PARP inhibitor
rucaparib, secondary reversion mutations in HR
genes restore the open reading frame and HR
activity to confer resistance.
See commentary. p. 997
See article. p. 1006

Analysis of Circulating Cell-Free
DNA Identifies Multicolonal
Heterogeneity of BRCA2 Reversion
Mutations Associated with
Resistance to PARP Inhibitors......... 999
D. Quigley, J.J. Alumkal, A.W. Wyatt, V. Kothari,
A. Foye, P. Lloyd, R. Aggarwal, W. Kim, E. Lu,
J. Schwartzman, K. Beja, M. Annala, R. Das,
M. Diolaiti, C. Prichard, G. Thomas, S. Tomlins,
K. Knudsen, C.J. Lord, C. Ryan, J. Youngren,
T.M. Beer, A. Ashworth, E.J. Small, and F.Y. Feng
Précis: Multicolonal BRCA2 reversion mutations were
detected in circulating cell-free DNA from two patients
with metastatic prostate cancer after PARP inhibitor
treatment, suggesting a mechanism of resistance.
See commentary. p. 997
See article. p. 984
See article. p. 1006

Circulating Cell-Free DNA to Guide
Prostate Cancer Treatment with
PARP Inhibition......................... 1006
J. Goodall, J. Mateo, W. Yuan, H. Mossop, N. Porta,
S. Miranda, R. Perez-Lopez, D. Dolling, D.R. Robinson,
S. Sandhu, G. Fowler, B. Ebbs, P. Flohr, G. Seed,
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Ibrutinib Unmasks Critical Role
of Bruton Tyrosine Kinase in
Primary CNS Lymphoma............. 1018
C. Grommes, A. Pastore, N. Palaskas, S.S. Tang,
C. Campos, D. Schartz, P. Codega, D. Nichol,
O. Clark, W.-Y. Hsieh, D. Rohle, M. Rosenblum,
A. Viale, V.S. Tabar, C.W. Brennan, I.T. Gavrilovic,
T.J. Kaley, C.P. Nolan, A. Omuro, E. Pentsova,
A.A. Thomas, E. Tsyvkin, A. Noy, M.L. Palomba,
P. Hamlin, C.S. Sauter, C.H. Moskowitz, J. Wolfe,
A. Dogan, M. Won, J. Glass, S. Peak, E.C. Lalana,
V. Hatzoglou, A.S. Reiner, P.H. Gutin, J.T. Huse,
K.S. Panageas, T.G. Graeber, N. Schultz,
L.M. Angelis, and I.K. Mellinghoff
Précis: The BTK inhibitor ibrutinib has activity in
patients with relapsed or refractory B-cell
lymphomas of the CNS, and dual treatment with
PI3K/mTOR inhibitors may enhance ibrutinib
efficacy in patients with CD79B-mutant tumors.
See commentary. p. 940

Discovery and Optimization of
HKT288, a Cadherin-6–Targeting
ADC for the Treatment of Ovarian
and Renal Cancers...................... 1030
C.U. Bialucha, S.D. Collins, X. Li, P. Saxena,
X. Zhang, C. Dür, B. Lafont, P. Prieur, Y. Shim,
R. Mosher, D. Lee, L. Oststrom, T. Hu, S. Blic, I.L. Rajlic,
V. Capka, W. Jiang, J.P. Wagner, G. Elliott, A. Veloso,
J.C. Piel, M.M. Flaherty, K.G. Mansfield, E.K. Meseck,
T. Rubic-Schneider, A.S. London, W.R. Tschantz,
M. Kurz, D. Nguyen, A. Bourret, M.J. Meyer, J.E. Faris,
M.J. Janatpour, V.W. Chan, N.C. Yoder, K.C. Catcott,
M.A. McShea, S. Sun, H. Gao, J. Williams, F. Hofmann,
Précis: The CDH6-targeting antibody–drug
conjugate HKT288 causes regression of patient-
derived xenografts of CDH6-overexpressing
ovarian and renal cancers.
PARP inhibitors (PARPi) have demonstrated activity in patients with mutations in homologous recombination (HR) genes such as BRCA1 and BRCA2. Three related studies identified HR gene reversion mutations that confer resistance to PARPi. Kondrashova and colleagues discovered secondary reversion mutations in BRCA1, RAD51C, and RAD51D in patients with PARPi-resistant ovarian cancer. Similarly, Quigley, Alumkal, and colleagues identified BRCA2 reversion mutations associated with PARPi resistance in circulating cell-free DNA (cfDNA) from two patients with prostate cancer. Finally, Goodall, Mateo, and colleagues found secondary reversion mutations in BRCA2 and PALB2 in cfDNA from patients with PARPi-resistant metastatic prostate cancer. Together, these studies demonstrate that HR gene reversion mutations can promote resistance to PARPi. For details, please see the article by Kondrashova and colleagues on page 984, the article by Quigley, Alumkal, and colleagues on page 999, and the article by Goodall, Mateo, and colleagues on page 1006.